Review of Literature
Peptic perforation is the most serious and important complication of gastroduodenal ulceration. The earliest mention of duodenal ulcer in the medical literature is in the London ‘Medico-Chisurgical Transaction’ of 1817. Mr. Travers there reports 2 cases of perforated duodenal ulcer.

In the second edition of Pathological and practical research on disease of the stomach by Dr. John Abercrombie five cases stored in literature are collected together.

The first clear description is usually attributed to Cruveilhier (1829) whose name it bore for many years as the round ulcer of Cruveilhier but Methew Baillie pictured the lesion in a series of engravings published in 1979. The first paper specially devoted to this subject appeared in 1861, it dealt solely with perforating ulcer and notes were given of cases collected from literature.

In 1894 H.P. Dean recorded the first successful case of perforating ulcer treated by operation, LA Dun followed
him. The results of these two cases drew conspicuous attention to the subject, and other success quickly followed. Wair gave an excellent summary of the early cases, together with a critical review of the whole subject of perforating duodenal ulcer in his presidential address to the American Surgical Association.

Rosenow (1921) in Mayo Clinic produced peptic ulceration in rabbits by the intravenous injection of streptococci from human ulcer. Levy (1920) produced similar results by injection of sterile broth. Braithwaite (1923) suggested a lymphatic infection. Seley and Colp (1941) have proved the presence of pathogens in peptic ulcer perforation.

Cushing's (1932) neurogenic theory in the causation of peptic ulcer is well documented. Mc Carrison (1924) has observed that the incidence of peptic ulcer is 50 times higher in South India than in North India. In 1936, it was pointed out by Mc Carrison, Somervell, and Orr that dietetic factors were of paramount importance in causation of peptic
ulcer. Diets poor in protein and vitamins A, B and C and fat have all been blamed.

Recently smoking has erupted up as an important etiological factor in the causation of peptic ulcer. In 1947, Jamieson et al studied the smoking habits of 437 cases of perforated peptic ulcer and concluded that heavy smoking was associated with severe symptoms. A carefully controlled study by Doll et al (1958) showed that smoking could be a factor in the production of peptic ulcer. Gastric secretion is stimulated with smoking has been proved by Gray 1930, Crohn (1938), Chrenfeld and Stutevart (1941) and Steigmenn, (1954).

Dodds and his associates (1934) produced chronic ulcer with perforation by oral and subcutaneous administration of pituitarin in rabbits, which produces mucosal ischemia by spasm. Mann and Williamson (1923) showed if the duodenal contents were diverted to the ileum and the jejunum exposed to undiluted gastric juice a typical
chronic peptic ulcer developed almost invariably, proving the importance of hyperacidity in the causation of peptic ulcer.

Genetic influences are important in predisposition to duodenal ulcer, which are as follows:

1) Duodenal ulcer is about three times more common in first-degree relations of ulcer patient that in general population.

2) A 50% concordance for duodenal ulcer has been observed in monozygotic twins as compared with 14% in dizygotic twins.

3) Individuals of blood group ‘O’ are about 37% more likely to develop duodenal ulcer than those with other blood groups.

4) An increase incidence of HLA b-5 antigens also has been identified in white males with duodenal ulcer.

5) The genetic trait with pepsinogen hypersecretion segregated as an autosomal dominant trait is hailed as a marker for predisposition to duodenal ulcers.
Duodenal ulcer is more frequent in patients with alcoholic cirrhosis, chronic renal failure and hyperparathyroidism. In general, duodenal ulcer patients have higher mean basal acid output and maximal acid output than do normal controls and significantly higher levels than present in patients with gastric ulcer.

There is evidence linking the recently isolated organism H. pylori. H. pylori has been isolated from the gastric mucosa in 90% of patients with duodenal ulcers, 70% with gastric ulcers and 60% with non-ulcer dyspepsia (Marshal et al, 1985). The pathogenic role of H. pylori has yet to be confirmed, current evidence suggests that this organism is probably on of the several contributory factors in pathogenesis of peptic ulceration.

As yet the story is still unfolding. Even so, enough is now known to consider getting some of the fruits of a decade of research into practice – to cure peptic ulcer disease with antimicrobial therapy rather than put patients on expensive long term acid-suppressing therapies.
It is not intended here to give a definitive review of all the information that exists on H. pylori and associations with peptic ulcer disease. Rather, this section is designed to provide sufficient background information to familiarise the reader with the subject. There are a number of excellent reviews which describe various aspects of peptic ulcer disease, dyspepsia and H. pylori (Blaser, 1990; Soll, 1990; Petereson, 1991; Graham, 1993; Pope, 1994).

As usual, an excellent overview comes from the non-science literature. The Economist of March 5, 1994 produced a remarkably concise review of the H. pylori story with some punchy comment. It refers to an economic analysis by Ammon Sonnenberg of the Medical College of Wisconsin, demonstrating that a 15-year treatment of ulcer with current drugs would cost $11,500 per patients, to which could be added at least $17,500 if surgery is needed. Eradicating H. pylori would cost less than $1,000. Says Sonnenbery "From an economic perspective, antibiotic therapy is the treatment
of choice”; says the Economist “It also makes people healthier”.

**H. PYLORI**

The presence of spiral - shaped micro - organism in stomach mucosa was described almost 100 years ago (quoted by Madan et al, 1988). Their presence was not really taken seriously until the late 1970s, when John Warren, a pathologist in Perth, Western Australia, noted the appearance of spiral bacteria overlaying gastric mucosa, and chiefly over inflamed tissue. Warren and Barry Marshall cultured these organisms in 1982 from 11 patients with gastritis; the story of the early part of the discovery of H. pylori is related by Marshall and is worth reading because of that (Marshall, 1989).

Originally called Campylobacter pyloridis. The name was changed to Camplyobacter pylori and then later to H. pylori as specific morphologic, structural and genetic features indicated that it should be placed in a new genus.
The organism is a motile, gram-negative, curved rod which is oxidase, catalase and urease positive.

Marshall and Warren were able to demonstrate a strong association between the presence of H. pylori and the finding of inflammation on gastric biopsy (Marshall & Warren, 1984). People who did not have gastritis did not have the organism, a finding confirmed in a number of studies (see below). Marshall elegantly fulfilled Koch’s postulates for the role of H. pylori in antral gastritis with self administration of H. pylori, and also showed that it could be cured by use of antibiotics and bismuth salts.

**EVIDENCE IMPLICATING H. PYLORI IN GASTRITIS AND PEPTIC ULCER**

There are a number of pieces of evidence:-

Voluntary ingestion of H. pylori resulted in chronic gastritis inflammations (notably type B gastritis almost universally present in duodenal ulcer), not all types.

There is a systemic immune response to H. pylori infection. H. pylori antibodies diminish with effective
antimicrobial therapy. Clearance of gastric inflammation with bismuth salts (bismuth has antimicrobial properties).

**ASSOCIATION OF H. PYLORI WITH EPIDEMIC GASTRITIS AND HYPOCHLORHYDRIA**

Another compelling piece of evidence comes from the epidemiology of gastritis and H. pylori infection. The pattern of H. pylori acquisition with age is identical to that of gastritis. Serological tests for H. pylori infection (circulating IgG and IgA antibodies measured by immunological methods) show that H. pylori infection is low in children, but rises dramatically in the fifth and subsequent decades, and that more than half of the population over 50 years is infected. This seems to be due to a continuous risk of infection (Veldhuyzen van Zanten et al, 1994). The prevalence of chronic gastritis with age is given alongside the serology results below:-
**H. PYLORI AND ULCERS**

A further early finding was that infection with H. pylori was almost 100% in those patients with duodenal ulcers, and approached that figure in patients with gastric ulcers. Collected data from studies published up to 1990 are shown below (from Blaser, 1990).

People who have developed peptic ulcer are much more likely to have had H. pylori infection up to 10 years previously (Normura et al, 1994), and studies of twins in Sweden has shown that there is a considerable genetic component in susceptibility to infection (Malaty et al, 1994),

**HOW DOES H. PYLORI CAUSE GASTRITIS AND ULCERS?**

H. pylori are motile, even in the highly viscous mucus layer in which they live. This may allow the organisms to evade both gastric motility and peristalsis, and to some extent gastric acidity also. The organism seems specifically to overlay gastric-type epithelial cells, whether in
the stomach or metaplastic in the duodenum; they will not overlay absorptive-type duodenal cells, even when these are metaplastic in the stomach. Although it is motile, it also may adhere to the gastric mucosa through specific adhesion mechanisms.

The secretion of large amounts of urease result in any urea in the environment being converted into ammonia— with the result that the intense acidity of the stomach may be ameliorated in the Micro environment surrounding the bacterium. The Michaelis constant of H. pylori urease is 0.4 mm. making it one of the lowest known for this enzyme, and allowing significant conversion of urea to ammonia at very low urea concentrations and, therefore, to work efficiently in the stomach.

About 50% of H. pylori strains produce cytotoxins (Crabtree et al, 1991b), of which some have been specifically linked to active gastritis and peptic ulceration. The strains isolated from patients with the most severe disease tend to be more likely to secrete these cytotoxins
than strains isolated from asymptomatic patients. These cytotoxins can cause local inflammation, though other secretions by organism, such as proteases and phospholipases, can attack and damage mucosal cell membranes. Weakening the gastric - mucosal barrier permits back - diffusion of hydrogen ions resulting in further tissue injury, as well as causing local immune responses to the organism.

There is also evidence that H. pylori infection is responsible for reducing the levels of ascorbic acid in the gastric juice; levels in infected patients were only 25% of those in non-infected subjects (Banerjee et al, 1994). Moreover, eradication of H. pylori resulted in a large increase in gastric juice ascorbate. The reversible lowering of gastric juice ascorbate may predispose to gastric cancer and peptic ulceration (Banerjee et al, 1994).

It is entirely likely that assays could be made available which detected antibody response to the aggressive strains of H. pylori or their associated damaging
cytotoxins. Such a development would allow for a much more simple therapeutic approach – if a test for such an aggressive strain proved positive in symptomatic or asymptomatic individuals, eradication would be a sensible first course of action.

**METHODS OF DIAGNOSING H. PYLORI INFECTION**

There are several methods which can be used to diagnose whether a patient is infected with H. pylori. They differ in being invasive or non-invasive. Simple or difficult, cheap or expensive. Though far from an exhaustive coverage, the main points of each method are given below.

**INVASIVE METHODS**

**CULTURE**

H. pylori can be cultured only when a specimen containing the pathogen has been obtained, and in his case that means obtaining a biopsy specimen at endoscopy. Methods of culture vary, but in general they involve homogenising the biopsy specimen and culturing the
homogenate on a variety of specialised agar plates at elevated temperatures for at least seven days.

Culture is generally regarded as the 'gold standard' for detecting a bacterium. For H. pylori, however, the success of the technique depends on local technique and access to facilities, and can be regarded as being no more than 60 – 90% sensitive, though being 100% specific; the cost of each test is high (DeCross & Puera, 1992; Perez et al, 1988).

**HISTOLOGY**

Histological examination of tissue biopsy samples (usually four, taken from different parts of the stomach lining) permits detection of the bacterium together with evaluation of tissue damage. Most infection can be detected with haematoxylin & eosin H&E results are not conclusive.

The sensitivity of Wright-Giemsa and Brown0Hopps stains has been shown to be 100%, compared with H&E (Madan et al, 1988), though histological detection of the organism has generally been considered to have lower
sensitivity at 80 – 95% with 100% specificity. The need for a number of biopsy specimens to be examined by experienced pathologist renders histology expensive, and it requires an invasive procedure.

**CLO Testing**

The CLO test is for Campylobacter-like organisms. At the time of endoscopy and biopsy, a pinch of tissue is removed and placed in a test solution containing urea, a pH colour reagent and a bacteriostatic agent. The presence of urease from H. pylori results in hydrolysis of neutral urea to alkaline ammonia, together with a pH change and a change in colour (usually from yellow to red).

In infected tissues the change occurs within about one hour, so that the results of the CLO test are often available while the patient is still at the endoscopy unit, meaning that therapy decisions can be made immediately. Though the test itself is inexpensive, it still requires an invasive procedure to obtain the sample. It has 90-95%
sensitivity and high specificity, and the overall cost is moderate.

**NON-INVASIVE TESTING**

**BREATH TESTING**

Urea breath testing is non-invasive, and a specific indicator of H. pylori infection (Atherton & Spiller, 1994). The procedure requires a patient to attend a centre fasting, to eat a standard meal and then ingest urea labeled with C-14 or C-13. The presence of large amounts of H. pylori urease results in the production of labeled carbon di-oxide, which is absorbed into the blood and excreted in the breath. Samples of breath are collected before and some time after the ingestion of labeled urea and the amount of labeled carbon di-oxide measured by mass spectrometry or radioactive counting.

While quite specific, few detection systems are readily available, and they do have a significant capital cost.
Breath samples can be sent by post to measuring centres, though this involves a necessary delay before results are available. Breath testing is both sensitive (at least 95%) and specific (at least 98%) with a moderate cost.

Breath testing has the important advantage of being both non-invasive, and being able to confirm H. pylori eradication about one month or so after treatment has ended, should that be necessary.

**ANTIBODY MEASUREMENT**

Patients infected with H. pylori have immunoglobulin antibodies to the organism. Tests for the detection of antibodies to H. pylori circulating in blood, or found in saliva, have excellent sensitivity and specificity of above 95% and are cheap and simple compared with invasive techniques (DeCross (Puera, 1992). They can give very quick results even within minutes of the first consultation, and are the only tests which are not likely to give false negative results in patients who have taken antibiotics, bismuth compounds
or omeprazole in the recent past (NIH Consensus Conference, 1994).

Because there are different strains of H. pylori, antigen for antibody manufacture is generally prepared by using preparations from several different strains. Antibody assays in blood have measured IgG and IgA antibodies which have been shown to be specific for H. pylori and not other gram-negative organisms (Perez-Perez et al, 1988). Where both IgG and IgA assays have been compared with other testing methods, like culture and/or histology, IgG assays tend to have slightly high sensitivity and specificity, and so anti-IgG methods tend to be favoured (Perez-Perez et al, 1988; Glassman et al, 1990; Crabtree et al 1991a).

The commercially available assays are of two sorts: either microtitre-plate assays for use in a laboratory, or near-patient testing devices. Both types of assay usually have a cut-off value set with control sera so that they differentiate patients with H. pylori infection from those who do not, rather than quantify the concentration or circulating
anti-H. pylori immunoglobulin. Laboratory based microtitre assays (Crabtree et al, 1991a) and near-patient testing devices (Pronovost et al, 1994) perform equally well compared with standard techniques.

Test for antibodies to H. pylori in saliva are equally effective as those for antibody in serum (Patel et al, 0994). In saliva IgG immunoglobulins must be measured, as measuring IgA antibodies does not distinguish positive from negative cases.

Antibody tests have high sensitivity and specificity when compared with other methods. They also have the advantage of being non-invasive, and near-patient versions are available which can produce results from a small finger prick of blood within a few minutes. The costs of antibody tests (bedside or laboratory) are much lower than any other methods.

At least one commentator has suggested that for H. pylori infection, serology testing may be the “gold standard” (Blaser, 1990). Essentially, every person who gastric biopsy
can be showed to harbour H. pylori has evidence of a systemic humoral immune response. Those in whom the organism cannot be detected by the other methods have a low false positive rate by serology. However, gastritis can be a patchy phenomenon and histologic biopsy and culture assess only a small area of the stomach, while serology in essence assays the entire stomach. “False-positive” serology may well, infact, reflect falsely negative biopsy results.

**QUANTITATION OF ANTIBODY TESTS**

Knowing how much antibody was present in the blood has not generally been thought to be helpful. Very high concentrations have been found in infected patients who also have gastric cancer (Forman et al, 1991), and more recently Nomura and colleagues (1994) found that there was a higher degree of association between H. pylori infection with higher levels of circulating antibodies. The extent of the elevation in this study was much lower than that seen by Forman and colleagues for gastric cancer.
Almost all studies have concentrated on demonstrating the presence of antibodies to H. pylori as a means of diagnosis of infection. Systematic attempts to correlated levels of antibody to particular disease states have not been conducted. It is interesting to speculate that tests which discriminate actual circulating concentrations of antibodies to H. pylori might increase significantly the diagnostic yield for both peptic ulcer disease and gastric cancer, thus making screening a viable option for these diseases.

**ANTIBODY TESTING AFTER H. PYLORI ERADICATION**

Titres of IgG and IgA in serum fall relatively slowly after H. pylori has been successfully eradicated. Thus six weeks after eradication titres fall by about 20-30%, but by six months, about 97% of patient have titres reduced by 50% or more from pre-treatment levels (Kosunen et al, 1992). Because of this slow reduction in antibody titres after successful eradication, serology testing is not generally useful in confirming the success of eradication within a few
weeks of treatment; urea breath tests and histology or culture after repeat endoscopy can make that confirmation, if needed. However, since H. pylori reinfection or regrowth can take place within the first six months after treatment, waiting at least six months before retesting may be a better option.

However, there is one report, albeit of a preliminary nature, which indicates that in saliva, antibody titres to particular H. pylori membrane antigen fall much more rapidly (Clancy et al, 1993). In a small number of patients it was showed that 83% had falls in salivary antibody titres of more than 50% within one month of successful eradication therapy. As an indicator of successful treatment, this is similar to standard methods for monitoring elimination.